Are blood flow measurements by means of Transcranial Doppler valid under different levels of end-tidal CO2? A high resolution MRI study at 7 Tesla of the middle cerebral artery diameter under hypo- and hypercapnic conditions

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TARGET AUDIENCE – Researchers in the field of cerebrovascular reactivity and Transcranial Doppler

PURPOSE – Transcranial Doppler (TCD) is a widely used and non-invasive measurement technique for cerebral blood flow velocity employed to monitor physiological responses. Velocity measured before and after a challenge, such as hypercapnia, sit-to-stand or head-up-tilt, are often interpreted as cerebral blood flow changes, assuming a constant vessel diameter[1]. However, carbon dioxide (CO_2) is a potent vasodilator and is not only frequently exploited as a physiological stimulus, but is also known to vary during many other challenges[2]. It could therefore be hypothesized that the assumption of constant diameter does not hold true during end-tidal CO_2-fluctuations ($PetCO_2$), although previous studies have been inconsistent[1,3,4]. The purpose of the current study was to investigate whether the diameter of the middle cerebral artery (MCA) changes upon $PetCO_2$ variations and if so to obtain a calibration curve for MCA-diameter changes as a function of $\Delta PetCO_2$. Such a calibration curve could be used to translate TCD velocity measurements more accurately into cerebral blood flow.

METHODS – Subjects: Nine healthy subjects (aged 21–30 years, 5 male, 4 female) were included, written informed consent was obtained and the protocol was approved by the local IRB. Subjects were asked to refrain from eating and drinking for two hours prior to the experiment. **Measurements:** An air mixture containing 21% oxygen, nitrogen and CO_2 varying from 0 to 8% was administered to the subject through a silicon face mask. $PetCO_2$ was measured with a cannula attached to the face mask and connected to a capnograph (Capnomac Ultima, Datex). **Protocol:** Four levels of $PetCO_2$, relative to the resting $PetCO_2$, were administered to the subjects: -1 kPa (hypocapnia), 0 kPa (normocapnia), +1 (mild) and +2 kPa (moderate hypercapnia). The order of $PetCO_2$-administration was randomized over subjects and $PetCO_2$ was kept constant while scanning. **MRI acquisition:** Measurements were performed on a 7 Tesla Philips MRI system. The MCA was located on orthogonally reconstructed axial 3D T1 scans. Subsequently, the high resolution 2D scan was positioned perpendicular to the MCA. To account for subject motion two dynamics were acquired. The dynamic with the better image quality was used in the event of subject motion, otherwise the average was used. Imaging parameters were: black blood T_2 Fast Spin Echo (FSE), TR/TE = 2000/116 ms, refocusing angle = 110°, FOV 240x180x5 mm, acquisition matrix 1200x900, voxel size 0.20x0.20x5.0 mm, FSE factor 12 with 4 startup echoes, scan duration ~5 min. **Data analysis:** Two independent observers, blinded to subject and CO_2-level, delineated the vessel lumen by means of an ellipse. Observer agreement was assessed with the Intraclass Correlation Coefficient (ICC), whereas vessel diameter and $PetCO_2$ were analysed with one-way repeated measures ANOVA. To be able to compare diameter changes between subjects, the diameters for each subject were normalized to the mean diameter for that subject. Polynomial models up to 4th order were fitted to the relative diameter versus ΔCO_2 and goodness-of-fit was assessed with the R-square (R^2) statistic adjusted for degrees of freedom.

RESULTS – All nine subjects completed the study; one scan at the moderate hypercapnia level was excluded from analysis due to poor image quality. Baseline $PetCO_2$ was 4.9±0.5 kPa, and the four induced $PetCO_2$ levels were 3.9±0.5, 5.1±0.6, 6.0±0.6 and 6.8±0.6 kPa. An example of a high resolution image of the MCA is shown in Figure 1A. The between-observer agreement was high, ICC=0.93, however there was a systematic difference of 0.16 mm ($p<0.02$, paired t-test) between the two observers. The average value of the two observers was used in subsequent analysis. Mean MCA diameters for the four conditions were 3.3±0.2, 3.3±0.2, 3.6±0.3 and 3.5±0.3 mm. Fig 1B shows the effect of $PetCO_2$ on the MCA diameter and the effect of $PetCO_2$ on the normalized diameter is depicted in Fig 1C. Relative to normocapnia, the normalized diameter decreased by 0.91% for hypocapnia and increased by 1.68% for mild and 6.97% for moderate hypercapnia. Post-hoc tests indicate that the normalized diameter at moderate hypercapnia differed significantly from hypo-, normo- and mild hypercapnia ($F(3,21)=18.1$, $p<0.05$, Dunn-Sidak corrected), however no other differences were found. The best fit was obtained for a quadratic model, $y = 0.013x^2 + 0.015x + 0.98$, with an adjusted R^2 of 0.63 (linear, cubic and 4th order models had an adj-R^2 of 0.50, 0.62 and 0.60 respectively).

DISCUSSION - This study indicates that moderate, but not mild, hypercapnia increases the MCA diameter in humans. No change was observed during hypocapnia. The observed trend can be approximated by a quadratic function of $\Delta PetCO_2$, shown in Figure 1C. For example, neglecting diameter changes of the MCA while increasing $\Delta PetCO_2$ from normacapnia to +2 kPa, would lead to an underestimation of the cerebral blood flow change by 17% (95% CI=11-22%).

CONCLUSION – When interpreting cerebral blood flow velocity changes measured with TCD as a proxy for cerebral blood flow changes, care must be taken since the assumption of constant MCA-diameter does not hold true when $PetCO_2$-changes approach moderate hypercapnia. In that case, no direct coupling between flow and flow velocity can be assumed and therefore we propose the use of a quadratic model to take MCA-diameter changes into account when translating blood flow velocity into blood flow changes under various levels of end-tidal CO_2.

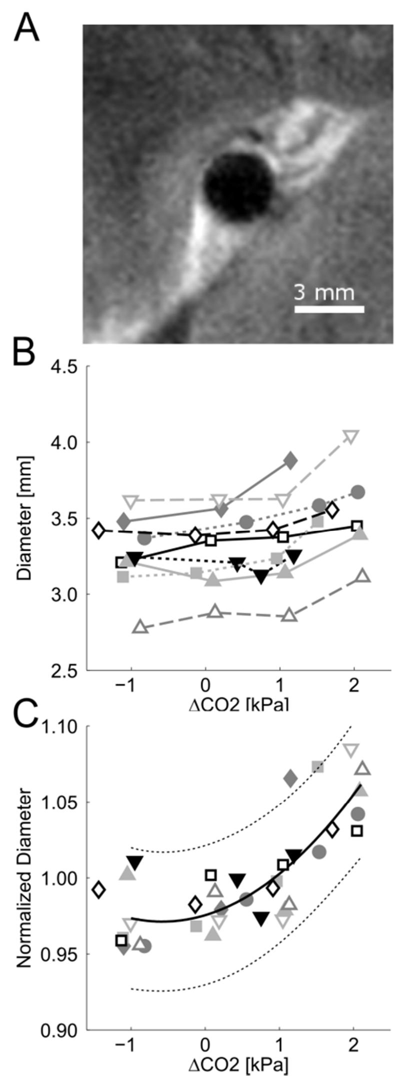

Figure 1: **A)** *High resolution scan perpendicular to the MCA;* **B)** *Effect of ΔCO_2 on MCA diameter;* **C)** *normalized diameter; fit of the quadratic model is indicated with a think line and dashed lines represent the 95% confidence interval. ΔCO_2 is relative to resting end-tidal CO_2 and individual subjects are represented by different symbols.*

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